UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,787	12/12/2003	Thierry Canton	FRAV2002/0036 US NP	3482

5487 7590 09/14/2007

ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	**PAPER NUMBER**
1623	

NOTIFICATION DATE	DELIVERY MODE
09/14/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi-aventis.com
andrea.ryan@sanofi-aventis.com

Office Action Summary	Application No.	Applicant(s)	
	10/734,787	CANTON ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-22 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-22 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 6/25/2007 has been received, entered and carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 1-18 and 23-24 have been canceled.

2. Claim 27 has been amended.

3. Remarks drawn to rejections under 35 USC 112, first paragraph and 103.

Claims 19-22 and 25-28 are pending in the case.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 19-22 and 25-28 for lack of enablement for prevention of Alzheimer's using the compounds and combinations of active agents instantly claimed is being maintained for reasons of record. Instant Claim 19 is drawn to prevention or treatment of Alzheimer's disease in a patient at risk of developing the disease or in the course of developing the said disease, comprising administering an effective amount of a compound having hypochloesterolemic activity. In instant claim 27, the recitation, "cholesterol synthesis inhibitors or γ and β amyloid β precursor protein (APP) secretase inhibitors" has been deleted. Claim 19 still recites prevention. Claim 19 also recites the broad terms, "compound having hypochloesterolemic activity", which are seen to include several compounds, known and unknown at the time of filing, having the said activity. Enablement is seen only for the treatment

of Alzheimer's disease using compounds of formula (IA) and its combination with ezetimibe and statins and not for prevention. Amendment to claim 27 alone is not seen to overcome the enablement rejection. Applicants have not set forth any significant arguments for the lack of enablement rejection of record.

The following rejection is made of record necessitated by amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-22 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frick et al (US 6,221,897) and Castaner et al (Drugs of the Future, 2000, 25(7), 679-685) in view of Refolo et al (Neurobiology of Diseases, 2001, 8, 890-899) all of record.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Frick et al teach compounds of formula I (col. 23, line 1 through col. 24, line 17), which is the same as the compound of formula IA as instantly claimed and pharmaceutical compositions comprising the compounds of formula I (col. 25, lines 57-59). Their compounds of formula I are also useful for lowering the serum cholesterol level (col. 3, lines 5-11). The suitable dosage is 0.02 to 50mg and the compositions are in a form for oral administration like capsules, tablets, etc. (col. 3, line 26 through col. 4, line 22). However, Fricke et al do not teach compositions comprising their compound of formula I in combination with a cholesterol uptake inhibitor.

Castaner teaches that ezetimibe (page 679, formula shown at top left) is a potent cholesterol absorption inhibitor (page 682, right column, pharmacological actions through page 683, left and right columns). This is same as cholesterol uptake inhibitor as recited in instant claim 27. According to Castaner, drugs used in the treatment of hyperlipidemia include cholesterol biosynthesis inhibitors like HMG-CoA reductase inhibitors (as recited in instant claim 27; page 680, right column, introduction through page 681, left column, bottom).

According to Refolo et al studies have shown that cholesterol may play an important role in the pathogenesis of Alzheimer's disease. A strong correlation between the amount of plasma cholesterol level and brain A-beta peptides and beta-amyloid was observed (page 890, abstract). These amyloid peptides are present in the neurite plaque of Alzheimer's patients (page 890, Introduction). However, Refolo et al do not teach or suggest the use of a biliary acid uptake inhibitor like compounds of instant formula IA for the said treatment.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art for reducing cholesterol level, which in turn is tied to Alzheimer's. See In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

Response to Applicants Arguments

The 103(a) rejection above is being advanced necessitated by amendment.

Applicants have traversed the 103(a) rejection made in the previous office action by arguing that:

1. Even though Fricke et al teach the very same compounds of formula (IA) used in the instant invention the combination of Fricke and Refolo would not motivate one of skill in the art to use a compound having hypochloesterolemic activity with virtually no blood-brain permeability to treat Alzheimer's disease as recited in instant claim 19 or a combination of said compounds and HMG-CoA reductase inhibitors. Refolo teaches away from the instant invention.

2. The biliary acid reuptake inhibitors are effective in an animal model of Alzheimer's disease by acting only through the regulation of plasma cholesterol level and do not penetrate into the brain.

Applicants' arguments are not found to be persuasive.

Fricke teaches the very same compounds that are used in the method of the instant invention. Applicants have also acknowledged this fact. According to Refolo et al studies have shown that cholesterol may play an important role in the pathogenesis of Alzheimer's disease. A strong correlation between the amount of plasma cholesterol level and brain A-beta peptides and beta-amyloid was observed (page 890, abstract). Hence from the teaching of Refolo, one of skill in the art will recognize that reducing the level of plasma cholesterol would be a method of treating Alzheimer's disease. Refolo is used to show the correlation between Alzheimer's and cholesterol levels. It is immaterial what type of compound Refolo uses and its mechanism of action.

Fricke teaches compounds as instantly claimed and they are well-known cholesterol reducing agents, and it is logical that the compounds of Fricke can be used for treating Alzheimer's by reducing cholesterol levels. Since the compounds of Fricke are same the compounds of the instant invention it is inherent that they do not penetrate the body. There is also no teaching by Fricke that they penetrate the blood-brain barrier either. Hence the combination of references does render the instant claims obvious.

Conclusion

Claims 19-22 and 25-28 are rejected

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

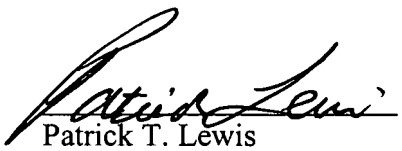
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK



Patrick T. Lewis
Primary Patent Examiner
Art Unit 1623